

# Indium-Trichloride Mediated Synthesis of 4,4-Dichlorotetrahydropyrans

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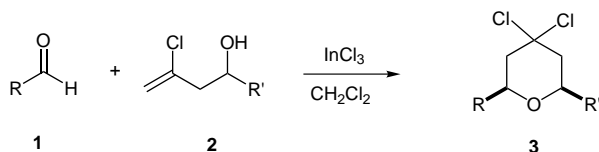
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**Abstract:** The cross-coupling of aldehydes with chloro homoallyl alcohols mediated by indium trichloride generated (*cis*) 2,6-disubstituted-4,4-(*gem*)-dichlorotetrahydropyrans smoothly with high diastereoselectivity.

**Key words:** Indium trichloride, Prins reaction, 4,4-dichlorotetrahydropyran, *gem*-dihalide.

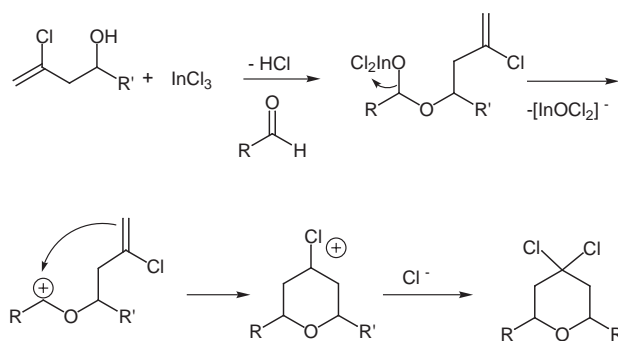
Recently, there is a considerable interest in using indium for organic transformations.<sup>1</sup> Indium-mediated carbon-carbon bond formations have been investigated intensively both in organic solvents<sup>2</sup> and in aqueous media.<sup>3</sup> Besides indium metal, indium halides have been shown to be useful Lewis catalysts.<sup>4</sup> They are even effective in aqueous medium.<sup>5</sup> Indium halides being Lewis acids also catalyze Prins-type cyclization reactions,<sup>6</sup> which involve the addition of olefins to aldehydes. Herein we wish to report that the cross-coupling between an aldehyde and a chloro homoallyl alcohol mediated by indium trichloride provides 4,4-dichloro-(*gem*)-dichloro-tetrahydropyran derivatives with high *cis*-diastereoselectivity (Scheme 1).



Scheme 1

Previously, during our investigation of indium mediated reactions in water, we have developed methods to synthesize various chloro homoallyl alcohols.<sup>7</sup> The speculation of the mechanism of the Prins-type cyclization that we reported earlier prompted us to synthesize *gem*-dihalo tetrahydropyrans by using these chloro homoallyl alcohols. Consequently, reaction of benzaldehyde with 3-chloro-1-phenyl-3-butene and indium trichloride in dichloromethylene at room temperature leads to the smooth formation of 2,6-diphenyl-4,4-dichlorotetrahydropyran in 65% isolated yield with a high diastereoselectivity. <sup>1</sup>H NMR measurement of the crude reaction mixture revealed that a major isomer (together with ca. 5% unidentified minor product) where both phenyl groups are *cis*- to one another is formed. From the symmetrical feature and the coupling constants (*J*=10.6 Hz) of the <sup>1</sup>H NMR measurements, it was determined that both phenyl substituents are equatorial (depending on the reaction substrate, a *J<sub>gauche</sub>* = 0–1.5

Hz was observed). Such stereoselectivity was most likely due to a thermodynamic control. Various 2,6-disubstituted dichlorotetrahydropyrans were synthesized similarly (Table 1). Aromatic aldehydes and their corresponding homoallyl alcohols reacted generating the corresponding symmetrically 2,6-disubstituted tetrahydropyran derivatives stereoselectively (entries 2–5).<sup>8</sup> The cross-cyclization between an aliphatic aldehyde and its corresponding homoallyl alcohol was equally successful (entry 6). In addition to the formation of symmetrical compounds, unsymmetrical 2,6-disubstituted 4,4-dichlorotetrahydropyrans were also readily accessible (entries 7–8).<sup>9</sup> Although the synthesis of the unsymmetrical aliphatic and aromatic substituted compounds is accessible from either aliphatic aldehydes reacting with aromatic homoallyl alcohols or aromatic aldehydes reacting with aliphatic homoallyl alcohols, it was found that the latter generally gave better yields and cleaner products. The mechanism of the cyclization products is illustrated in Scheme 2. Indium trichloride mediated a hemi-acetal formation. A subsequent C–O bond cleavage resulted in the formation of carbocation that is stabilized by the oxygen. Intramolecular cyclization of the carbocation generated a six-membered ring and a chlorine-stabilized carbocation. Nucleophilic attack of the cation by the chloride ion generated the *gem*-dihalides. Currently, we are exploring the application of reactions related to the present study in natural product synthesis.



Scheme 2 Proposed Mechanism for the Indium Trichloride-Mediated Formation of 4,4-Dichloro-tetrahydropyrans

**Table 1** Indium Trichloride Mediated Synthesis of 4,4-dichlorotetrahydropyrans

Entry	Aldehyde	Homoallyl Alcohol	Product	Yield (%)
1				65
2				70
3				66
4				50
5				52
6	$n\text{-C}_7\text{H}_{15}\text{CHO}$			65
7				58
8				52

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- (8) A typical experimental procedure: To a mixture of benzaldehyde (53 mg, 0.50 mmol) and 3-chloro-1-phenyl-3-buten-1-ol (91 mg, 0.50 mmol) in 3 mL of  $\text{CH}_2\text{Cl}_2$ , which was pre-dried with 4Å molecular sieve overnight, was added indium chloride (133 mg, 0.60 mmol) in one portion. The reaction flask was capped with a rubber septum and the mixture was stirred at room temperature for 8h. The reaction mixture was concentrated *in vacuo* to give the crude product which was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 10 : 1) (yield 101 mg, 65%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz):  $\delta$  2.48 (dd,  $J$  = 11.5, 13.5 Hz, 2H), 2.84 (d,  $J$  = 14.4 Hz, 2H), 5.0(d,  $J$  = 10.6 Hz, 2H), 7.34-7.50 (m, 10H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100MHz):  $\delta$  52.9, 76.5, 87.2, 126.0, 128.1, 128.6, 140.4ppm; FTIR(film): 3062, 3029, 2966, 2874, 1495, 1453, 1346, 1294, 1245, 1205, 1151, 1067, 1029, 758, 698  $\text{cm}^{-1}$ ; Anal. Calc'd. for  $\text{C}_{17}\text{H}_{16}\text{Cl}_2\text{O}$ : C, 66.5; H, 5.2; Found: C, 66.9; H, 5.4.
- (9) 2-Heptyl-6-phenyl-4,4-dichlorotetrahydropyran: IR (Film): 3030, 2926, 2855, 1495, 1454, 1328, 1206, 1157, 1063, 841, 777, 756 and 697  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR(400 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  = 0.87(t,  $J$  = 6.8 Hz, 3H), 1.23-1.50(m, 12H), 2.12(dd,  $J$  = 13.8, 10.9 Hz, 1H), 2.28(dd,  $J$  = 13.8, 10.9 Hz, 1H), 2.55(dt,  $J$  = 13.8, 2.1 Hz, 1H), 2.70(dt,  $J$  = 13.8, 2.1 Hz, 1H), 3.83(m, 1H), 4.72(dd,  $J$  = 10.9, 2.1 Hz, 1H), 7.26-7.36(m, 5H).  $^{13}\text{C}$  NMR(100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  = 50.9, 52.9, 74.6, 75.9, 87.8, 14.1, 22.6, 25.3, 29.2, 29.5, 31.8, 35.2, 125.8, 127.8, 128.5, 140.6. Anal. Calc'd for  $\text{C}_{18}\text{H}_{26}\text{Cl}_2\text{O}$ : C, 65.7; H, 8.0. Found: C, 65.5; H, 8.6.

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